REMARKS

Claims 1-26 are pending in the application. Claims 17 and 26 have been cancelled by this amendment. Claim 27 was cancelled previously. New claims 28-37 have been added to the application. Therefore, claims 1-16, 18-25, and 28-37 are at issue.

Claim 1 has been amended to incorporate the features of originally filed, and now-cancelled, claim 17. Claims 7 and 16 have been amended to correct the dependency of these claims. Claim 24 has been amended to delete the feature of 10 mg of active compound per tablet. This feature now is recited in new claim 31. Claim 24 serves as support for new claim 31.

New claims 28-30 recite additional particle sizes for the free drug. Support for new claims 28-30 can be found at page 8, lines 14-27 of the specification.

New claims 32-34 recite amounts of active compound present in a tablet. Support for new claims 32-34 can be found in Example 3 (containing 2.5 mg of active compound) and at page 13, lines 9-18 of the specification.

Cancelled claim 26 has been rewritten as new claim 35. New claim 36 recites that the sexual dysfunction is male erectile dysfunction. Support for new claim 36 can be found in the specification at page 4, lines 26-29. New claim 37 recites the particle size of the free drug as well as formulation ingredients. Support for claim 37 is found in claim 1 and claim 17 (cancelled herein).

The specification is objected to for failing to contain an abstract. In response, applicants submit

an abstract, on a separate sheet, concurrently with this amendment. The specification also has been amended at page 10 to delete "hydroxyethylcellulose" and "hydroxybutylmethylcellulose" as hydrophilic binders.

Claims 1-4, 6, 7, 9, 11-16, and 26 stand rejected under 35 U.S.C. §102(b) as being anticipated by WO 97/03675 (WO '675). Claims 5, 8, 10, 19, and 22-25 stand rejected under 35 U.S.C. §103 as being unpatentable over WO '675. For the reasons set forth below, it is submitted that all pending claims are patentable over WO '675.

In particular, claim 17 was not included in these rejections under 35 U.S.C. §102(b) and 35 U.S.C. §103 based on WO '675. In view of the amendment to claim 1, which incorporates the features of claim 17, the rejections of the claims over WO '675 alone are moot and should be withdrawn.

Claims 17, 18, 20, and 21 stand rejected under 35 U.S.C. §103 as being unpatentable over WO '675 in view of WO 96/38131 (WO '131) and U.S. Patent No. 4,721,709 ('709). Claim 17 has been cancelled herein, and the features of claim 17 incorporated into claim 1. For the reasons set forth below, it is submitted that this rejection is in error and should be withdrawn.

The patentability of all pending claims over WO '675 has been discussed above. In addition, claim 1 recites a particle size for Compound (I), which the examiner explicitly states that WO '675 *fails* to teach (see page 5 of the Office Action).

Furthermore, the presently claimed formulations are a result of substantial research directed to

providing a stable composition that effectively delivers the claimed compound (i.e., Compound (I)) *in vivo*. Compound (I) is a highly water-insoluble drug and its formulation into a pharmaceutical composition that effectively delivers the drug is not straightforward. As a result of applicants' investigation, a pharmaceutical composition that is physically stable, and that demonstrates improved dissolution and *in vivo* absorption has been achieved.

In view of the above, the '675 patent has failed to teach or suggest the present invention as a whole. Accordingly, it is submitted that the pending claims would not have been obvious over WO '675.

The secondary WO '131 and '709 references do not overcome the deficiencies of WO '675 for the reasons stated below.

WO '131 is directed to improving the bioavailability of poorly water-soluble drugs, like Compound (I), by forming a coprecipitate dispersion. WO '131, therefore, teaches forming a coprecipitate and *avoiding* the free form of a poorly water-soluble drug, like Compound (I), to improve dissolution of the drug. In addition, the examiner also states at page 5 of the Office Action that WO '131 "fails to teach the claimed particle sizes."

In contrast, the present claims recite incorporating Compound (I) of a certain particle into the formulation as a *free* drug. Rather than rendering the present claims obvious, after reading WO '131, a person skilled in the art would have had no motivation or incentive (a) to incorporate a free form of Compound (I) into a pharmaceutical formulation or (b) to provide a

free drug of the claimed particle size, let alone utilize *both* of these features. In fact, WO '131 actually teaches away from using a free form of Compound (I) and is silent with respect to particle size.

Seth et al. '709 also fails to cure the deficiencies of the combined teachings of WO '675 and WO '131. The '709 patent merely teaches fine particle size benzodiazepine drugs adsorbed onto a carrier. These drugs are substantially different from Compound (I). The '709 patent, at column 6, lines 40 through column 7, line 40 teaches how to adsorb the benzodiazepine drug onto a carrier by dissolution and precipitation. The adsorbed drug then is incorporated into a formulation. The '709 patent, however, fails to teach any formulations that would help overcome the deficiencies of WO '675 and WO '131, taken alone or in combination, to render the present claims obvious.

Accordingly, there is no teaching in the '709 patent that would lead a person skilled in the art to modify WO '675 and WO '131 in a manner to arrive at a presently claimed formulation as a whole.

In addition, the examiner misapplies applicants' incorporation of U.S. Patent No. 4,605,517 ('517) by reference. The '517 patent is incorporated by reference merely for the purpose of instructing persons reading the present specification how to measure particle size. See specification, page 8, lines 28-32. The '517 patent is not referenced for a method of preparing the present compositions. Preparation of the present compositions is illustrated in the examples, and applicants do not rely upon the method of U.S. Patent No. 4,605,517.

Furthermore, the examiner is focusing on the method of manufacturing the adsorbed drug disclosed in the '709 patent. Applicants are *not* claiming a method of manufacturing a pharmaceutical composition, but are claiming a composition. The presently claimed compositions are neither taught nor suggested by the combination of WO '675, WO '131, and the '709 patent. Accordingly, it is submitted that the rejection of the claims over the combination of WO '675, WO '131, and the '709 patent should be withdrawn.

Claims 1-26 also stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over copending application Nos. 10/031,531 and 10/031,463. Applicants traverse this rejection and submit that the rejection should be withdrawn.

In issuing an obviousness-type double patenting rejection, it is the *claims* of the present application that must be compared to the claims of U.S. Application Nos. 10/031,531 and 10/031,463. Applicants submit that in determining obviousness-type double patenting, the question to be considered is stated in *In re Vogel*, 164 U.S.P.Q. 619, 622 (CCPA 1970), i.e., "Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent?" The CCPA goes on to indicate that, "In considering the question, the patent disclosure may not be used as prior art." For the reasons set forth below, the present obviousness-type double patenting rejection cannot be maintained.

As stated above, the present claims are directed to a stable pharmaceutical formulation that

demonstrates improved dissolution and improved *in vivo* absorption of Compound (I). The invention resides in the claimed formulation comprising an active compound provided as a free drug having a certain particle size in combination with ingredients, and amounts of ingredients, which achieve this result (see amended claim 1). Among the presently claimed features of the invention are a pharmaceutical formulation containing Compound (I) as a free drug, a small particle size of Compound (I), a solid formulation, a solid tablet, and a capsule containing dry, free-flowing particles of the formulation.

Application No. 10/031,531 is directed to capsules containing a solution or a dispersion of Compound (I). The formulations presently claimed in 10/031,531 directed to a suspension formulation of Compound (I) in a liquid, and are completely different from the present claims. The problem solved in 10/031,531 was to solubilize Compound (I) in a solution, or to provide a stable dispersion of Compound (I) in a liquid. Neither of these problems is considered in the present application, which is directed to *solid* (particulate) formulations containing Compound (I).

A person skilled in the art could not possibly arrive at a presently claimed composition after reading the claims of 10/031,531. A simple comparison of the present claims in 10/031,531 to the presently claimed formulations shows no relation between the compositions. The compositions in the 10/031,531 claims are totally different from the presently claimed formulations, and the 10/031,531 claims contain no teachings or suggestions that would lead a person

skilled in the art to modify the compositions claimed in 10/031,531 in a manner that would provide a presently claimed formulation as a whole regardless of whether the formulation is a capsule or solid. Moreover, the formulations are as fundamentally different as a solid formulation versus a liquid or dispersion formulation, before even considering the substantial differences between formulation ingredients.

The claims of application No. 10/031,463 are directed to Compound (I) in a reduced particle size. The present claims are directed to *formulations* containing free Compound (I) having a certain particle size, as well as other ingredients as recited in claim 1. The claims of application No. 10/031,463 merely recite the composition containing the small particle size of Compound (I) and one or more pharmaceutically acceptable carrier, diluent, or excipient. However, these claims fail to recite any *specific* carriers, diluents, or excipients as well as the form of formulation (tablet or capsule) as presently claimed, thus the 10/031,463 claims provide no teachings or suggestions that would lead a person skilled in the art to the presently claimed formulations as a whole.

In view of the above, it is submitted that the present claims are not obvious over the claims of application Nos. 10/031,531 and 10/031,463, which contain claims directed to inventions entirely different from the presently claimed invention. Therefore, it is submitted that the obviousness-type double patenting rejection of the present claims over the claims of application Nos. 10/031,531 and 10/031,463 is in error and should be withdrawn.

In response to the examiner's request to show that the inventions of the present application and application Nos. 10/031,531 and 10/031,463 were commonly aimed at the type of invention applicants provide the following assignment information.

Serial No.	Assignment Recordal	Provisional Application
10/031,464 (present application)	Reel 12877, Frame 177 May 8, 2002	60/146,924 filed April 3, 1999
10/031,463	Reel 13114, Frame 703 July 20, 2002	60/147,048 filed August 3, 1999
10/031,531	Reel 12818, Frame 640 April 15, 2002	60/146,924 filed August 3, 1999

The three applications are commonly owned by Lilly ICOS LLC. Applicants fail to see any interfering subject matter between the present claims and the present claims of 10/031,463 and 10/031,531. The recitation of application No. 10/031,151 in the Office Action is assumed to be a typographical error.

In summary, it is submitted that the present claims are in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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Hawley's Condensed Chemical Dictionary

ELEVENTH EDITION

Revised by

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polymer, stereospecific. (stereoregular). A polymer whose molecular structure has a definite spatial arrangement, i.e., a fixed position in geometrical space for the constituent atoms and atomic groups comprising the molecular chain, rather than the random and varying arrangement that characterizes an amorphous polymer. Achievement of this specific steric (three-dimensional) structure (also called tacticity) requires use of special catalysts such as those developed by Ziegler and Natta about 1950. Such polymers are wholly or partially crystalline. Synthetic natural rubber, cis-polyisoprene, is an example of a stereospecific polymer made possible by this means. There are five types of stereospecific (or stereoregular) structures: cis, trans, isotactic, syndiotactic, and tritactic.
See also catalyst, stereospecific.

polymer, syndiotactic. See syndiotactic polymer.

polymer, synthetic. See polymer.

polymer, water-soluble. Any substance of high molecular weight that swells or dissolves in water at normal temperature. These fall into several groups, including natural, semisynthetic, and synthetic products. Their common property of water solubility makes them valuable for a wide variety of applications as thickeners, adhesives, coatings, food additives, textile sizing, etc.
See specific entries.
(1) *Natural*. This type is principally comprised of gums, which are complex carbohydrates of the sugar group. They occur as exudations of hardened sap on the bark of various tropical species of trees. All are strongly hydrophilic. Examples are arabic, tragacanth, karaya.
(2) *Semisynthetic*. This group (sometimes called water-soluble resins) includes such chemically treated natural polymers as carboxymethylcellulose, methylcellulose, and other cellulose ethers, as well as various kinds of modified starches (ethers and acetates).
(3) *Synthetic*. The principal members of this class are polyvinyl alcohol, ethylene oxide polymers, polyvinyl pyrrolidone, polyethyleneimine.

polymethacrylate resin. See acrylic resin, methyl methacrylate.

polymethylbenzene. See durene and pseudocumene, the two members of this group with some commercial production and use.

polymethylene polyphenylisocyanate. A polymer of diphenylmethane-4,4′ diisocyanate.

polymethylene wax. See wax, polymethylene.

poly-4-methylpentene-1.
Properties: High resistance to all chemicals except carbon tetrachloride and cyclohexane, excellent heat resistance, high clarity and light transmittance. Temperature limit 170C, d 0.83.
Use: Laboratory ware (beakers, graduates, etc.), electronic and hospital equipment; food packaging, especially types subject to high temperature such as trays for TV dinners, etc.; light reflectors.

poly(methyl vinyl ether). See polyvinyl methyl ether.

polymorphism. See allotropy.

polymyxin. CAS: 1406-11-7. Generic term for a series of antibiotic substances produced by strains of *Bacillus polymyxa*. Various polymyxins are differentiated by the letters A, B, C, D, and E. All are active against certain gram-negative bacteria. Polymyxin B is most used.
Properties: All are basic polypeptides, soluble in water; the hydrochlorides are soluble in water and methanol, insoluble in ether, acetone, chlorinated solvents, and hydrocarbons. Permissible food additives.
Use: Medicine (antibiotic), beer production.

polynuclear. Descriptive of an aromatic compound containing three or more closed rings, usually of the benzenoid type, e.g., sterols.
See also polycyclic, nucleus (3).

polyol. A polyhydric alcohol, i.e., one containing three or more hydroxyl groups. Those having three hydroxyl groups (trihydric) are glycerols, those with more than three are called sugar alcohols, with general formula $CH_2OH(CHOH)_n CH_2OH$, where $_n$ may be from 2 to 5. These react with aldehydes and ketones to form acetals and ketals.
See also alcohol, glycerol.

polyolefin. A class or group name for thermoplastic polymers derived from simple olefins, among the more important are polyethylene, polypropylene, polybutenes, polyisoprene and their copolymers. Many are produced in the form of fibers. This group comprises the largest tonnage of all thermoplastics produced.

polyorganosilicate graft polymer. An organoclay to which a monomer or an active polymer has been chemically bonded, often by the use of ionizing radiation. An example is the bonding of styrene to a polysilicate containing vinyl radicals, resulting in the growth of polystyrene chains from the surface of the silicate. Such complexes are stable to organic solvents. They have consid-

erable use potential
as ablative agents,
draulic fluids.
See also organoclay,

"Polyox."[214] TM for
ethylene oxide polym
in the 100,000 to se
Use: Textile warp size,
hair spray, toothpast
film, adhesives.

polyoxadiazole. A pol
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ter) of polyisophthali
high temperature tol
made from it may be

polyoxamide. A nylon
oxalic acid and diami

polyoxetane. See oxeta

polyoxyethylene. See

polyoxyethylene fatty ac

polyoxyethylene (40) n
ene glycol stearate).
A mixture of the mo
of mixed polyoxyethy
ing free glycols. The n
sented as: $H(OCH_2CH$
40).
Properties: Waxy, light
congealing range 39–4
hol, ether and aceton
and vegetable oils.
Grade: USP.
Use: Ointments, emulsi
tive.
See also polysorbate.

polyoxyethyleneoxyprop
A polymer of ethyle
(ethylene oxide, propy
Use: Solvent.

polyoxyethylene (8) ste
A mixture of the mor
acid and mixed polyox
average polymer lengt
Properties: Cream-colo
solid at 25C, faint, fatty
fatty taste. Soluble in t
ethanol.
Use: Emulsifier in bake
See also polysorbate.